SCIENTIFIC OPINION

Scientific Opinion on the safety and efficacy of pantothenic acid (calcium D-pantothenate and D-panthenol) as a feed additive for all animal species based on a dossier submitted by Lohmann Animal Health[1, 2]

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)[3,4]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The use of calcium D-pantothenate in feed and of D-panthenol in water for drinking is safe for all animal species and categories. The use of calcium D-pantothenate and D-panthenol as nutritional additives does not give rise to concern for consumers. Since no data on acute inhalation toxicity has been provided, inhalation of dust is considered as potentially hazardous. D-panthenol being currently only available in liquid preparations, the FEEDAP Panel does not anticipate any inhalation hazard. Because of the lack of data, calcium D-pantothenate is considered as a skin and eye irritant and a skin sensitiser. D-Panthenol is regarded as a skin and eye irritant in rabbits, and allergic rashes in humans have been reported following its topical use. A risk for the environment resulting from the use of pantothenic acid in animal nutrition is not foreseen. Due to its established nutritional role in domestic animals, calcium D-pantothenate is regarded as an effective source of pantothenic acid. D-Panthenol is considered a pro-vitamin essentially bioequivalent to pantothenic acid.

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KEY WORDS

Nutritional additive, vitamins and pro-vitamins, pantothenic acid, calcium D-pantothenate, D-panthenol, safety

[1] On request from the European Commission, Question No EFSA-Q-2011-00256, adopted on 11 October 2011.

[2] This scientific opinion has been edited following the provisions of Article 8(6) and Article 18 of Regulation (EC) No 1831/2003. The modified sections are indicated in the text.

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[4] Acknowledgement: The Panel wishes to thank the members of the Working Group on Vitamins, including Annette Schuhmacher, for the preparatory work on this scientific opinion.

Suggested citation: EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP); Scientific Opinion on the safety and efficacy of pantothenic acid (calcium D-pantothenate and D-panthenol) as a feed additive for all animal species based on a dossier submitted by Lohmann Animal Health. EFSA Journal 2011;9(11):2409. [15 pp.]. doi:10.2903/j.efsa.2011.2409. Available online: www.efsa.europa.eu/efsajournal

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SUMMARY

Following a request from the European Commission, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety and efficacy of pantothenic acid in the form of calcium D-pantothenate as an additive to feed and of D-panthenol as an additive to water for drinking for all animal species.

D-Pantothenic acid is the only naturally occurring and biologically active form of the vitamin. D-Panthenol is a synthetic pro-vitamin which is oxidised *in vivo* to pantothenic acid. D-Pantothenic acid is a component of coenzyme A, an essential coenzyme in a variety of chemical reactions involved in the energy metabolism; in particular, coenzyme A is required in the synthesis of essential fatty acids, carbohydrates, cholesterol, porphyrins and the neurotransmitter acetylcholine.

Oral administration routes of D-panthenol via feed or water for drinking are considered as bioequivalent.

The FEEDAP Panel considers that the use of calcium D-pantothenate in feed and of D-panthenol in water for drinking is safe for all animal species and categories.

The use of calcium D-pantothenate and D-panthenol as nutritional additives does not give rise to concern for consumers.

Since no data on acute inhalation toxicity has been provided, inhalation of dust is considered as potentially hazardous. D-panthenol being currently only available in liquid preparations, the FEEDAP Panel does not anticipate any inhalation hazard. Because of the lack of data, calcium D-pantothenate is considered as a skin and eye irritant and a skin sensitiser. D-Panthenol is regarded as a skin and eye irritant in rabbits, and allergic rashes in humans have been reported following its topical use.

Pantothenic acid occurs widely in nature. Its use in animal nutrition is not expected to substantially increase the concentration in the environment. Therefore, a risk for the environment resulting from the use of pantothenic acid in animal nutrition is not foreseen.

Due to its established nutritional role in domestic animals, calcium D-pantothenate is regarded as an effective source of pantothenic acid. D-Panthenol is considered a pro-vitamin essentially bioequivalent to pantothenic acid.

The FEEDAP Panel recommends that specifications for calcium D-pantothenate and D-panthenol when used as additives should follow those defined by the European Pharmacopeia.

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BACKGROUND

Regulation (EC) No 1831/2003[5] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of a feed additive shall submit an application in accordance with Article 7; in addition, Article 10(2) of that Regulation specifies that for existing products within the meaning of Article 10(1), an application shall be submitted in accordance with Article 7, at the latest one year before the expiry date of the authorisation given pursuant to Directive 70/524/EEC for additives with a limited authorisation period, and within a maximum of seven years after the entry into force of this Regulation for additives authorised without a time limit or pursuant to Directive 82/471/EEC.

The European Commission received a request from the company Lohmann Animal Health GmbH & Co KG[6] for (i) authorisation of a new use (i.e. use in water for drinking) of pantothenic acid in the form of D-panthenol and (ii) re-evaluation of authorisation of pantothenic acid in the form of calcium D-pantothenate, when used as a feed additive for all animal species (category: nutritional additive; functional group: vitamins, pro-vitamins and chemically well-defined substances having similar effect) under the conditions mentioned in Table 1.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive) and under Article 10(2) (re-evaluation of an authorised feed additive). EFSA received directly from the applicant the technical dossier in support of this application.[7] According to Article 8 of that Regulation, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. The particulars and documents in support of the application were considered valid by EFSA as of 20 April 2011.[8]

Pantothenic acid (calcium D-pantothenate and D-panthenol) has been authorised without a time limit under Council Directive 70/524/EEC[9] for its use for all animal species as a nutritional additive.

The Scientific Committee on Food issued an opinion on the tolerable upper intake level of pantothenic acid (SCF, 2002). The Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) published an opinion on Pantethine as source for pantothenic acid added as a nutritional substance in food supplements (EFSA, 2008).

TERMS OF REFERENCE

According to Article 8 of Regulation (EC) No 1831/2003, EFSA shall determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animal(s), consumer, user and the environment and the efficacy of the product pantothenic acid in the form of calcium D-pantothenate and D-panthenol, when used under the conditions described in Table 1.

[5] OJ L 268, 18.10.2003, p. 29.
[6] Lohmann Animal Health GmbH & Co KG, Heinz-Lohmann-Str 4, D-27472, Cuxhaven, Germany.
[7] EFSA Dossier reference: FAD-2010-0030.
[8] A new mandate was received in EFSA in March 2011.
[9] OJ C 50, 25.2.2004, p. 1.

Table 1: Description and conditions of use of the additive as proposed by the applicant

Additive	Pantothenic acid
Registration number/EC No/No (if appropriate)	
Category(-ies) of additive	Nutritional additive
Functional group(s) of additive	Vitamins, provitamins and chemically well defined substances having a similar effect

Description			
Composition, description	Chemical formula	Purity criteria (if appropriate)	Method of analysis (if appropriate)
a) Calcium D-pantothenate b) D-Panthenol	a)$C_{18}H_{32}CaN_2O_{10}$ b) $C_9H_{19}NO_4$	a) min 98 % b) min 98%	a)Ph.Eur. 5th, monograph 0470 b)Ph.Eur. 5th, monograph 0761

Trade name (if appropriate)	-
Name of the holder of authorisation (if appropriate)	-

Conditions of use				
Species or category of animal	Maximum Age	Minimum content	Maximum content	Withdrawal period (if appropriate)
		mg/kg of complete feedingstuffs		
All animal species and categories	-	-	-	-

Other provisions and additional requirements for the labelling	
Specific conditions or restrictions for use (if appropriate)	-
Specific conditions or restrictions for handling (if appropriate)	-
Post-market monitoring (if appropriate)	-
Specific conditions for use in complementary feedingstuffs (if appropriate)	-

Maximum Residue Limit (MRL) (if appropriate)			
Marker residue	Species or category of animal	Target tissue(s) or food products	Maximum content in tissues
-	-	-	-

ASSESSMENT

This opinion is based in part on data provided by a single company involved in the production of pantothenic acid. It should be recognised that this data from a single applicant covers only a fraction of existing additives containing pantothenic acid. The composition of the additives is not subject of the application. The FEEDAP Panel has sought to use the data provided together with data from other sources to deliver an opinion and to produce recommendations for the authorisation, which would secure the safety of future uses of pantothenic acid in the form of calcium D-pantothenate and D-panthenol as feed additives.

1. Introduction

Pantothenic acid, previously called vitamin B_5, is N-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-β-alanine. D-Pantothenic acid is the only naturally occurring and biologically active form. D-Pantothenic acid is a component of coenzyme A, an essential coenzyme in a variety of chemical reactions involved in the energy metabolism; in particular, coenzyme A is required in the synthesis of essential fatty acids, carbohydrates, cholesterol, porphyrins and the neurotransmitter acetylcholine.

Pantothenic acid in the form of calcium D-pantothenate and D-panthenol is included in the European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. It is authorised without a time limit in application of Article 9t (b) of Council Directive 70/524/EEC[10] concerning additives in feedingstuffs (2004/C 50/01) for its use in all animal species as a nutritional additive.

The applicant asks for the re-evaluation of the use of calcium D-pantothenate as additive to feed for all animal species and categories without restrictions on age, (withdrawal) time and content in feedingstuff. The applicant is also seeking authorisation for a new use of D-panthenol in water for drinking.

Pantothenic acid is authorised for use in food (Regulation (EC) No 1925/2006,[11] amended by Regulation (EC) No 1170/2009)[12] and in food supplements (Directive 2002/46/EC, Annex II),[13] for addition for specific nutritional purposes in foods for particular nutritional uses (Regulation (EC) No 953/2009),[14] to processed cereal based foods and baby foods for infants and young children (Directive 2006/125/EC, Annex IV)[15] and to infant formulae and follow-on formulae when reconstituted as instructed by the manufacturer (Directive 2006/141/EC, Annex III).[16] Pantothenic acid (as vitamin B_5), is also listed as a pharmacologically active substance in veterinary medicinal products and is not subject to maximum residue levels when used in food-producing animals (Commission Regulation (EU) No 37/2010).[17] D-Panthenol is authorised in cosmetics as skin conditioner (Directive 76/768/EEC, Annex 4).[18]

Calcium pantothenate and dexpanthenol (D-panthenol) are described in the European Pharmacopeia (PhEur) as Monographs (MG) 0470 and 0761, respectively.

2. Characterisation

Free pantothenic acid and its sodium salt are chemically unstable, and therefore the usual pharmaceutical preparation is the calcium salt (calcium pantothenate). The alcohol, panthenol, is a synthetic form which can be oxidised *in vivo* to pantothenic acid.

[10] OJ C 50, 25.2.2004, p. 1.
[11] OJ L 404 30.12.2006, p. 26.
[12] OJ L 314 1.12.2009, p. 36.
[13] OJ L 183 12.7.2002, p.51.
[14] OJ L 269, 14.10.2009, p.9.
[15] OJ L 339 6.12.2006, p. 16.
[16] OJ L 401 30.12.2006, p. 1.
[17] OJ L 15, 20.1.2010, p. 1.
[18] OJ L 262, 27.09.1976, p. 169.

2.1. Characterisation of the additive

2.1.1. Calcium D-pantothenate

Calcium D-pantothenate (IUPAC name: calcium bis[3-[[*(2R)*-2,4-dihydroxy-3,3-dimethylbutanoyl] amino]propanoate], synonyms: vitamin B_5, vitamin B_5 calcium salt, calpan) is identified by the CAS number 137-08-6 and the EINECS number 205-278-0. The structural formula of calcium D-pantothenate is shown in Figure 1.

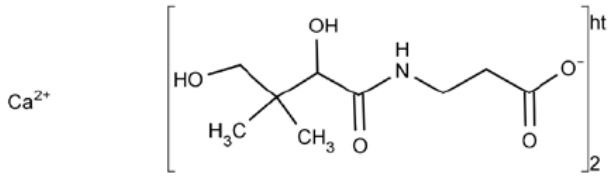

Figure 1: Structural formula of calcium D-pantothenate

The molecular formula of calcium D-pantothenate is $Ca[C_9H_{16}N_2O_5]_2$ and its molecular weight is 476.53. It has a melting point of about 200 °C with decomposition, a density of 1.32 g/cm^3 and a bulk density of 0.57–0.67 g/cm^3. It is freely soluble in water (1 g dissolves in about 2.8 mL at 25 °C).

The additive subject of this application is a whitish powder, slightly hygroscopic. The additive contains by specifications at least 98.0 % of dried substance (loss on drying < 3.0 %), in compliance with PhEur (MG 0470). The analysis of five batches of the additive showed an average content of calcium D-pantothenate of 99.6 ± 0.05 % (loss on drying 1.6–2.1 %).[19]

The applicant provided the results of the analysis of impurities in five batches of the additive.[18] The residual organic solvents (methanol) were compliant with VICH thresholds. The known impurity (PhEur, MG 0470) 3-aminopropionic acid was < 0.5 %. Chloride was below 200 mg/kg and heavy metals (expressed as lead) below 20 mg/kg, both complying with PhEur MG 0470.

The applicant provided data on particle size distribution and dusting potential for one batch of calcium D-pantothenate. The critical particle size fraction below 50 µm measured by laser diffraction was 7 % and the dusting potential 1.1 g/m^3.[20]

2.1.2. D-Panthenol

D-Panthenol (IUPAC name: 2,4-dihydroxy-N-(3-hydroxypropyl)-3,3-dimethylbutanamide; synonyms: dexpanthenol, vitamin B_5) is identified by the CAS number 81-13-0 and the EINECS number 201-327-3. The structural formula of D-panthenol is shown in Figure 2.

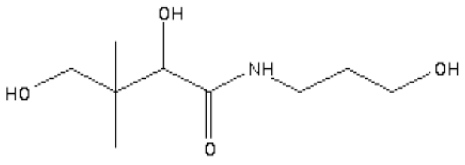

Figure 2: Structural formula of D-panthenol

[19] Technical dossier/Section II and supplementary information January 2011/Annex 2.20.
[20] Technical dossier/Section II /Annex 2.03 and supplementary information January 2011/Annex 3.01.

The molecular formula of D-panthenol is $C_9H_{19}NO_4$ and its molecular weight is 205.25. It has a boiling point of 118 °C, a flash point of 143 °C and a density of 1.16 g/cm^3. It is freely soluble in water.

The additive subject of this application is a colourless or slightly yellowish, viscous hygroscopic liquid. The additive contains by specifications at least 98.0 % active substance with reference to the anhydrous substance (water < 1.0 %), in compliance with PhEur (MG 0761). The analysis of five batches of the additive resulted in an average of 99.5 ± 0.15 % D-panthenol (loss on drying 0.3–0.4 %).[21]

The applicant provided the results of the analysis of impurities in five batches of the additive.[20] The residual organic solvents (methanol) were compliant with VICH thresholds. The known impurity (PhEur, MG 0761) 3-aminopropanol was < 0.5 % and heavy metals (expressed as lead) below 20 mg/kg, both complying with PhEur MG 0761.

2.2. Manufacturing process[22]

The manufacturing processes of calcium D-pantothenate and D-panthenol are fully described in the dossier submitted by the applicant.

2.3. Stability and homogeneity

2.3.1. Calcium D pantothenate

2.3.1.1. Shelf life

Calcium D-pantothenate (three batches, stored in plastic bags) was demonstrated to have a shelf life of 36 months at 25 °C. Shelf life under accelerated conditions at 40 °C was shown for three batches of the product for six months.[23]

2.3.1.2. Stability in premixtures and feed

According to the data published in the literature (Coelho, 2002), the stability of calcium D-pantothenate in premixtures depends on the presence of trace elements and choline, with an average loss per month ranging from 0.04 % (vitamin premix without trace elements and choline) to 5.5 % or even to 8 % (vitamin premix with both trace elements and choline), according to Whitehead (2002).

Coelho (2002) reports that the average monthly loss of calcium D-pantothenate in pelleted and extruded feed is 1.8 %. Marchetti et al. (1999) investigated the stability of crystalline calcium D-pantothenate added to commercial fish feed. Initial concentrations of 226 mg/kg were reduced to 201 mg/kg after pelleting (by 11 %) and to 194 mg/kg after extrusion (by 14 %). When stored in paper bags at room temperature, the concentrations in pelleted fish feed were 194, 174 and 150 mg/kg after 30, 90 and 180 days, respectively, with a loss of 23 % after 90 days. In extruded feed, corresponding figures were 171, 152 and 142 mg/kg after 30, 90 and 180 days, respectively, with a loss of 33 % after 90 days.

One batch of a broiler premixture containing 12 g calcium D-pantothenate/kg (no choline chloride added) was shown to be stable for at least six months when stored at 25 °C. In a further study, three batches of a pig premixture (1 % inclusion rate) containing choline chloride showed no reduction on the content of calcium D-pantothenate after six months when stored at 20 °C.[24]

Stability of calcium D-pantothenate was also investigated in two batches of pig feed after pelleting and storage of feed (20 °C). After 12 weeks of storage, recovery ranged 83–91 %. Stability in broiler feed

[21] Technical dossier/Section II and supplementary information January 2001/Annex 2.20.
[22] This section has been edited following the provisions of Article 8(6) and Article 18 of Regulation (EC) No 1831/2003.
[23] Technical dossier/Section II.
[24] Technical dossier/Section II and supplementary information January 2011/Annexes 2.24 and 2.25.

could be estimated from the results of a stress test conducted under accelerated conditions with a dosage of calcium D-pantothenate ten-fold higher than that used under practical condition (225 mg/kg). No loss of calcium D-pantothenate was observed in mash feed and upon pelleting at temperatures up to 95 °C and for up to 12 minutes.[25]

2.3.2. D-Panthenol

2.3.2.1. Shelf life

D-Panthenol (three batches, stored in polyethylene bags) was demonstrated to have a shelf life of 36 months at 25 ± 2 °C. Shelf life under accelerated conditions at 40 ± 2 °C was shown for three batches of the product for six months.[26]

2.3.2.2. Stability in water for drinking

The stability of the additive D-panthenol in water (three batches) was demonstrated when added at concentrations of 600–750 mg/L for 24 hours at 20–25 °C.[27]

2.3.3. Homogeneity

Based on a statistical method (Jansen, 1992), the coefficient of variation for homogeneity of calcium D-pantothenate in poultry feed was calculated to be around 6.2 %. However, this method has been developed to test the working accuracy of mixing equipments.

D-panthenol is freely soluble in water and therefore homogeneity in water for drinking does not need to be demonstrated.

2.4. Physico-chemical incompatibilities or interactions

No physico-chemical incompatibilities or interactions have been reported between calcium D-pantothenate or D-panthenol and feed materials, carriers, other approved additives or medicinal products when the additive was added to premixtures and feed. No such incompatibilities or interactions are expected. However, since calcium D-pantothenate is rapidly destroyed in water by acids (and alkalis), the simultaneous use of acids and calcium D-pantothenate in water for drinking should be avoided.

2.5. Conditions of use

Calcium D-pantothenate and D-panthenol are intended for use in all animal species and categories without a maximum content and a withdrawal period. Calcium D-pantothenate is intended for use in feed (premixtures, complete or complementary feed), D-panthenol in water for drinking only.

2.6. Evaluation of the analytical methods by the European Union Reference Laboratory (EURL)

EFSA has verified the EURL report as it relates to the methods used for the control of calcium D-pantothenate and D-panthenol in animal feed. The Executive Summary of the EURL report can be found in the Appendix.

3. Safety

According to Regulation (EC) No 429/2008, tolerance, metabolism and residue, and toxicological (with concern to consumer safety) studies are not required for vitamins, pro-vitamins and chemically defined substances having similar effects which are already authorised as feed additives under

[25] Technical dossier A/Section II and supplementary information January 2011/Annexes 2.26 and 2.27.
[26] Technical dossier A/Section II.
[27] Technical dossier A/Section II and supplementary information January 2011/Annex 2.28.

Directive 70/524/EEC and which do not have the potential to accumulate, which the FEEDAP Panel considers is the case for pantothenic acid.

3.1. Safety for the target species

According to the NRC (1987), oral doses of 10000 mg/kg bw are well tolerated in animals. The FEEDAP Panel found no more recent studies (searching Medline[28] and Toxnet[29]) that would modify the NRC conclusion.

Requirements for pantothenic acid (NRC, see McDowell, 2000) are in the range of 7–12 mg/kg for pigs and 2–11 (15) mg/kg for poultry, 10–50 mg/kg for fish and 0.4–5 mg/kg feed for pets. Vitamin supplementation of commercial compound feed is mostly oriented towards recommendations, which are in the range of 8–20 mg/kg for pigs, 10–15 mg/kg for poultry, 30–50 mg/kg for fish and 8–14 mg/kg feed for pets (AWT, 2002). A survey on vitamin supplementation of commercial feeds for pigs and poultry in Europe (Belgium, Denmark, Germany, Italy, Netherlands, Portugal, Spain, United Kingdom) identified a range of 0–35 mg pantothenic acid as commercial use levels (Gropp, 1994; Whittemore et al., 2002).

It is concluded that pantothenic acid is safe for the target animals having a wide margin of safety (approaching 100 compared to the requirements/recommendations).

3.2. Safety for the consumer

Owing to the lack of systematic oral dose response intake studies and the very low toxicity of pantothenic acid, no UL could be derived by the Scientific Committee on Food (SCF, 2002). The UK Food Standards Agency (FSA, 2003) for guidance purposes, identified a supplemental daily intake of 200 mg (equivalent to 3.3 mg/kg bw/day for a 60-kg adult), in addition to that present in the diet, as not being expected to produce adverse effects in the general population. Assuming a maximum dietary intake of about 10 mg/person/day (rounded from the 97.5th percentile), this would equate to a total intake of 210 mg/person/day, or 3.5 mg/kg bw/day for a 60-kg adult.

A number of foods of animal origin are considered good sources of pantothenic acid, such as fish and chicken muscle, and milk; liver, kidney and egg yolk are considered as particularly rich sources. Approximately 80 % of pantothenic acid in animal tissues is incorporated in coenzyme A. Studies investigating the effect of feed supplementation on pantothenic acid levels in edible tissues and products are rather limited. A study performed by Pearson et al. in 1946 compared tissue levels in chickens fed 4 and 16 mg/kg pantothenic acid complete feed: deposition in liver was essentially unaltered, while levels in muscle approximately doubled (6.5 and 8.4 vs. 11.3 and 17.2 mg/kg in breast and leg, respectively). Other findings report that the levels in eggs can be influenced by dietary supplementation (Pérez-Vendrell et al., 2004; Johnson and Korver, 2008): e.g. supplemental levels of 7.5 and 10 mg/kg feed led to deposition of approximately 15 and 18.5 mg/kg, respectively, in the whole egg.

Considering the very low toxicity of pantothenic acid, the available data do not suggest the recommended feed supplementation levels would pose any concern for consumer safety. Therefore, the FEEDAP Panel considers the use of pantothenic acid as nutritional additive in animal feed as safe for consumers.

[28] http://www.ncbi.nlm.nih.gov/pubmed/
[29] http://toxnet.nlm.nih.gov/

3.3. Safety for the user

3.3.1. Effects on the respiratory system

Calcium D-pantothenate showed more than 7 % of particles with diameters < 50 µm and a dusting potential of 1.1 g/m^3. Since no data on acute inhalation toxicity has been provided, inhalation of dust is considered as potentially hazardous.

D-Panthenol is currently only available in liquid preparations to be used only for addition to water for drinking. The FEEDAP Panel does not anticipate any inhalation hazard from such use.

3.3.2. Effects on the eyes and skin

Because of the lack of data, calcium D-pantothenate is considered as a skin and eye irritant and skin sensitiser.

D-Panthenol is described in the Material Safety Data Sheet as a skin and eye irritant in rabbit. Allergic skin rashes have been reported in humans following its topical use (Roberts et al., 2006).

3.4. Safety for the environment

Pantothenic acid occurs widely in nature. Its use in animal nutrition is not expected to substantially increase the concentration in the environment. Therefore, a risk for the environment resulting from the use of pantothenic acid in animal nutrition is not foreseen.

4. Efficacy

According to Regulation (EC) No 429/2008, efficacy studies are not required for vitamins, pro-vitamins and chemically defined substances having similar effects which are already authorised as feed additives under Directive 70/524/EEC and which do not have the potential to accumulate in the body, which the FEEDAP Panel considers is the case for pantothenic acid.

Calcium D-pantothenate has about 92 % the biological activity of D-pantothenic acid; panthenol is described as a pro-vitamin and is mostly converted to pantothenic acid (Pfaltz, 1943, Rubin et al., 1948).

Pantothenic acid has been globally used in animal nutrition for decades. Clinically evident deficiency is very rare in field conditions, but sub-clinical deficiency with lower production and reproductive performance may occur. Data on requirement, allowances and recommendations (see Section 3.1) for feed supplementation are easily accessible as standard literature for animal nutrition experts.

5. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation[30] and Good Manufacturing Practice.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

Oral administration routes of D-panthenol via feed or water for drinking are considered as bioequivalent.

The use of calcium D-pantothenate in feed and of D-panthenol in water for drinking is safe for all animal species and categories.

[30] OJ L 35, 8.2.2005, p. 1.

The use of calcium D-pantothenate and D-panthenol as nutritional additives does not give rise to concern for consumers.

Calcium D-pantothenate showed a potential for inhalation exposure to particles of respirable size. Since no data on acute inhalation toxicity has been provided, inhalation of dust is considered as potentially hazardous. D-panthenol being currently only available in liquid preparations, the FEEDAP Panel does not anticipate any inhalation hazard. Because of the lack of data, calcium D-pantothenate is considered as a skin and eye irritant and a skin sensitiser. D-Panthenol is regarded as a skin and eye irritant in rabbits, and allergic rashes in humans have been reported following its topical use.

Pantothenic acid occurs widely in nature. Its use in animal nutrition is not expected to substantially increase the concentration in the environment. Therefore, a risk for the environment resulting from the use of pantothenic acid in animal nutrition is not foreseen.

Due to its established nutritional role in domestic animals, calcium D-pantothenate is regarded as an effective source of pantothenic acid. D-Panthenol is considered a pro-vitamin essentially bioequivalent to pantothenic acid.

RECOMMENDATIONS

The FEEDAP Panel proposes to adjust calcium D-pantothenate and D-panthenol specifications to PhEur MG 0470 and MG 0761, respectively, considering purity, substance-related impurities and other impurities.

When giving a warranty for stability in premixtures, the manufacturer should consider the effect of choline chloride. The FEEDAP Panel recommends therefore including a corresponding warning under other provisions of the authorisation (e.g. 'Stability of calcium D-pantothenate may be reduced in premixtures containing choline chloride').

DOCUMENTATION PROVIDED TO EFSA

1. Pantothenic acid as a feed additive for all animal species. June 2010. Submitted by Lohmann Animal Health GmbH & Co KG.

2. Pantothenic acid as a feed additive for all animal species. Supplementary information. January 2011. Submitted by Lohmann Animal Health GmbH & Co KG.

3. Evaluation report of the European Union Reference Laboratory for Feed Additives on the methods(s) of analysis for calcium D-pantothenate and D-panthenol.

4. Comments from Member States received through the ScienceNet.

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APPENDIX

Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis for calcium D-pantothenate and D-panthenol[31]

In the current application authorisation is sought for *Pantothenic acid* under Articles 4(1) and 10(2), under the category of 'nutritional additives' functional group 3(a), 'vitamins, pro-vitamins and chemically well defined substances having a similar effect' according to Annex I of Regulation (EC) No 1831/2003. Specifically, authorisation is sought for the use of *Pantothenic acid* for all animal species and categories. The *feed additive* to be registered is in the form of two active components: *Calcium-D-Pantothenate* and *D-Panthenol*. *Calcium-D-Pantothenate* is a white to almost white, spray dried or crystalline powder, slightly hygroscopic, freely soluble in water, with a minimum content of 98%. It is intended to be used in *premixtures* and *feedingstuffs*. *D-Panthenol* is highly viscous transparent or yellowish liquid at room temperature, freely soluble in water, with a minimum purity of 98%; it is intended to be used only in *water*. No minimum or maximum concentrations of the *feed additive* in *feedingstuffs* or *water* are proposed by the Applicants.

For the determination of *Calcium-D-Pantothenate* in the *feed additive* the Applicants (FAD-2010-0030 and 2010-0073) proposed the European Pharmacopoeia method, based on potentiometric titration with perchloric acid and identification by specific optical rotation. The EURL considers this method suitable to be used within the frame of official control.

For the determination of *Calcium-D-Pantothenate* in *premixtures* and *feedingstuffs* the Applicant (FAD-2010-0073) proposed a single laboratory validated and further verified method, based on Reverse Phase High-Performance Liquid Chromatography coupled to a single-quadrupole mass selective detector (RP-HPLC-MS). The following performance characteristics were reported:

- for *premixtures*: - a relative standard deviation of *repeatability* (RSD_r) ranging from of 1.7 to 2.4%; and - a *recovery* rate (R_{Rec}) ranging from 103 to 106%;

- for *feedingstuffs* (containing the *Calcium-D-Pantothenate* at a concentration from 30 to 60 mg/kg): - RSD_r ranging from of 2 to 4.7%; and - R_{Rec} ranging from 120 to 124%.

Based on the performance characteristics presented, the EURL recommends for official control the single laboratory validated and further verified method using RP-HPLC-MS, submitted by the Applicant, to determine *Calcium-D-Pantothenate* in *premixtures* and *feedingstuffs.*

For the determination of *D-Panthenol* in the *feed additive* the Applicants (FAD-2010-0030 and 2010-0073) proposed the European Pharmacopoeia method, based on titration with perchloric acid and potassium hydrogen phthalate and identification by specific optical rotation and infrared spectroscopy. The EURL considers this method suitable to be used within the frame of official control.

For the determination of *D-Panthenol* in *water* the Applicant (FAD-2010-0073) proposed a single laboratory validated and further verified method, using Reverse Phase High-Performance Liquid Chromatography (RP-HPLC), coupled to UV detector. The following performance characteristics were reported in water containing *D-Panthenol* at 10 mg/L:

- RSD_r ranging from of 0.27 to 0.95%;

- a relative standard deviation of *intermediate precision* (RSD_{int}) ranging from of 0.3 to 0.97%;

- R_{Rec} ranging from 99 to 101%;

- a limit of detection (LOD) and a limit of quantification (LOQ) of 0.9 mg/L and

3 mg/L, respectively.

[31] The full report is available on the EURL website. http://irmm.jrc.ec.europa.eu/SiteCollectionDocuments/FinRep-FAD-2010-0073.pdf

Based on the performance characteristics presented the EURL recommends for official control the single laboratory validated and further verified RP-HPLC-UV method, submitted by the Applicant, to determine *D-Panthenol* in *water*.

Further testing or validation of the methods to be performed through the consortium of National Reference Laboratories as specified by Article 10 (Commission Regulation (EC) No 378/2005) is not considered necessary.